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The Cough Hypersensitivity Syndrome: A Novel Paradigm for Understanding Cough

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Abstract For many years patients with chronic cough have been investigated in an attempt to diagnose the cause of the cough. Here I suggest that the overwhelming majority of patients with chronic cough have a single diagnosis: cough hypersensitivity syndrome. This is demonstrated by the homogeneous nature of the clinical history and investigational results of patients attending cough clinics. The hypersensitivity facet of the syndrome is demonstrated by objective testing with capsaicin and other protussive agents. Within the cough hypersensitivity syndrome there are different phenotypes. Those patients with a predominantly Th2-type immune response will develop eosinophilic inflammation and either cough-variant asthma or eosinophilic bronchitis. Those with predominantly heartburn symptoms will have a phenotype that reflects GERD and cough. However, the similarities between the different phenotypes far outweigh differences in a unifying diagnosis of the cough hypersensitivity syndrome, providing a more rational understanding of chronic cough.

Keywords Chronic cough · Airway hypersensitivity · Cough hypersensitivity syndrome

Introduction

It was not until the fourth quarter of the last century that it was realised that most patients presenting with chronic cough do not exhibit many of the features of conventional lung disease. The early reports from newly established clinics for the diagnosis and treatment of patients with chronic cough quickly identified a variety of causes for this syndrome [1]. The first diagnosis to be identified was asthma [2]. However, this was unlike the classic atopic asthma with an onset in childhood and a marked wheezing and bronchoconstriction. Cough-variant asthma had a very different clinical profile. It tended to be late onset, it was not always associated with marked atopy, particularly to common aeroallergens, and in particular it was not associated with marked bronchoconstriction. Patients were characterized by sputum eosinophilia and had bronchial hyperresponsiveness to methacholine but little in the way of bronchodilator response to β-agonists since bronchoconstriction was not a major feature. Subsequently, another group of patients with eosinophilic-led airway disease was described [3]. The discoverers of eosinophilic bronchitis were naturally keen to highlight the differences between this disease and cough-variant asthma [4, 5]. However, in reality, the difference consists of an absence of bronchial hyperresponsiveness in the eosinophilic bronchitis group. There is no doubt that patients with eosinophilic bronchitis differ from those with classic asthma. This has been very elegantly demonstrated on histological grounds with the mast cells being located in different compartments of the airway [6]. Asthma is characterized by mast cell infiltration of airway smooth muscle in contrast to the eosinophilic bronchitis group. However, the differentiation between eosinophilic bronchitis and cough-variant asthma appears less strong, relying on the presence or absence of the poorly understood phenomenon of bronchial hyperresponsiveness.

The second diagnosis to arise from the assessment of patients with chronic cough was postnasal drip syndrome (PNDS, or more recently labeled the upper airways cough syndrome) [7]. Here the patient with chronic cough

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complains of nasal symptoms, particularly a feeling of something running down the back of the throat. Whether this symptom represents a discrete clinical entity is much debated. A transatlantic division of opinion has been present for well over 200 years. The European opinion tended to suggest that PNDS was a symptom of some other underlying condition, whereas in the Americas PNDS achieved the status of a syndrome [8]. With regard to chronic cough, however, the diagnosis of PNDS as the cause of the chronic cough relied on the therapeutic response to first-generation antihistamines. In particular, the response to dexbrompheniramine and other alkyl amines was considered proof of the PNDS as a cause of cough. Subsequent investigations have demonstrated that these agents may actually block the cough reflex irrespective of the cause of cough [9].

The final component in the triad of causes of cough is gastroesophageal reflux disease (GERD). GERD had been well characterized by gastroenterologists as a major cause of heartburn and the criteria for the intense liquid acid reflux required to produce this symptom have been extensively documented [10]. While some patients with chronic cough fulfilled the heartburn-derived paradigm for GERD, there were a considerable number who had marginal abnormalities on conventional pH and manometry testing. Even with the incorrect heartburn-related paradigm, an increasing number of patients were recognised as having cough related to GERD. There have been attempts to change the criteria for looking at reflux-related cough. Esophageal impedance measurements, which detect liquid or gaseous nonacid reflux, have been studied and Sifrim et al. [11] have shown that at least a third of coughing episodes in chronic cough patients are nonacid- or weakly acid-related. Thus, by crudely applying the paradigm worked out for reflux-associated heartburn to chronic cough, many patients are denied a diagnosis of reflux because they have little or no heartburn.

In the absence of a clear diagnostic test for asthmatic cough, PNDS, or reflux cough, there is now a group of patients that clinicians have been unable to pigeonhole to a particular diagnostic category. These patients have acquired the epithet of "idiopathic cough" [12]. Incidence of this "disease" differs among centres depending on how rigorously the diagnostic criteria for the triad of cough diagnoses discussed above are applied. Thus, if a positive DeMeester score is required to diagnose GERD as a cause of cough, then a patient may be placed in the idiopathic cough category even though postprandial coughing, characteristic of reflux, may be a prominent feature.

Hypersensitivity in Chronic Cough

The clinical history of patients with chronic cough contains numerous examples of hypersensitivity of the upper airways. Patients almost universally complain of cough being precipitated by a change in atmosphere, such as moving from a room of one temperature to another. Similarly, there is hypersensitivity to even minute amounts of irritants such as strong smells, cleaning fluids, and perfumes. Tobacco smoke is another common precipitant. A recent patient complained that her hypersensitivity was such that even walking past the exterior smoking area of her workplace would precipitate a coughing attack, even though there were no smokers present. The hypersensitivity component has been well characterized in an elegant series of articles by Millqvist [13, 14]. She demonstrates marked hypersensitivity through the inhalation of ethanol. In these studies the patients are characterized as having unexplained respiratory symptoms. In fact, virtually all patients have a chronic cough. In patients presenting to cough clinics, this hypersensitivity has been extensively demonstrated with capsaicin inhalation [15]. As in the normal population, women are more sensitive than men and the hypersensitivity disappears if there is successful treatment of the chronic cough.

The pathophysiological basis of this hypersensitivity appears to be upregulation of the TRP nociceptors. In the case of capsaicin hypersensitivity this is mediated through the TRPV1 [16]. Some studies show increased TRPV1 immunofluorescence in neurones from biopsies in chronic coughers [17]. We have demonstrated upregulation of the TRPV1 receptor by inflammation and the receptor becomes expressed in non-neuronal as well as neuronal tissue [18]. Indeed, there is expression of TRPV1 within the cytoplasm, presumably on the cytoplasmic membranes, inferring that hypersensitivity is achieved by altering cellular responsiveness. While TRPV1 can be defined as a hot receptor, giving capsaicin its pungency, another member of the temperature-sensitive TRP family has been implicated in cough hypersensitivity. The fact that TRP temperature receptors have been utilised in nociception for cough explains the change-in-atmosphere complaint made by most chronic cough patients.

The very cold receptor TRPA1 has recently caused much excitement by its potential for being a more generalised nociceptor producing cough. TRPA1 is able to bind and be activated by a wide range of noxious substances known to cause cough [19]. Thus, acreolin, the noxious component of smoke, binds TRPA1 in both cellular systems and isolated vagus nerve preparations. We have recently demonstrated that cinnamaldehyde, another TRPA1 agonist, activates TRPA1 in vitro and by inhalational challenge in man causing a dose-related cough response. If upregulation of TRPA1 in disease causing chronic cough can be demonstrated, then the mechanism of this hypersensitivity so vividly described by the patients can be established, and, more importantly, potentially therapeutic strategies could be developed to combat TRP nociceptor hypersensitivity.

Cough Hypersensitivity Syndrome

With rare exceptions patients with chronic cough present with a strikingly similar clinical history. Part of this commonality arises from the almost universal hypersensitivity seen in these patients. Another aspect is cough precipitated by various physiological and pathophysiological manoeuvres. Thus, cough on phonation, cough precipitated during or soon after eating, and the positional nature of the cough being worsened by lying down and precipitated by rising in the morning are all extremely common in the chronic cough population [20]. This striking similarity in the clinical history of patients with chronic cough is reflected in the results of investigations. Thus, when the airways are sampled either by bronchioalveolar lavage or by biopsy, there appears to be no distinct patterns in terms of histological features [21], cellular profile, and inflammatory markers [22, 23]. Could the paradigm that one should look for the cause of the chronic cough in various established diseases be an incorrect way of viewing the problem? The analogy here is with chronic obstructive pulmonary disease. Thirty years ago when the effect of smoking on the airways was finally recognised, various phenotypes were identified such as chronic bronchitis and emphysema. There is no doubt that pink puffers and blue bloaters do exist. However, it has been almost universally accepted that smoking-related airways disease should be labeled with the overarching diagnosis of COPD. This recognises that the majority of patients have a mixed picture, with some having predominantly emphysema and others chronic bronchitis. The utility of recognising these different facets within a common syndrome of smoking-related airways disease provides greater understanding than treating them as separate entities. Similarly, with chronic cough we had been trying to find the "cause" of the cough from within our established lexicon of diseases.

Because of the commonality in symptoms and pathophysiological findings in patients with chronic cough, I believe them to be suffering from a single entity, cough hypersensitivity syndrome. As with COPD, there will be different phenotypes within this condition. Those with a greater predisposition to a Th2-type response to a given noxious stimulus may develop cough-variant asthma with a predominance of eosinophilic inflammation. Those with predominantly acid heartburn will be labeled as having reflux cough and those with predominantly nasal symptoms will be said to have PNDS. The overall diagnosis, however, remains the cough hypersensitivity syndrome. This obviates the need for the use of the term idiopathic cough since the patients have cough hypersensitivity syndrome without an obvious phenotype.

Perhaps the major reason for the almost universal use of COPD, even when there are clinically obvious phenotypes, is that the stimulus causing COPD was easily identified: tobacco smoking. Unfortunately, there is no agreed upon single stimulus that precipitates cough hypersensitivity. Chung and Pavord [24] have proposed that a variety of precipitants such as pollution, drugs, or infection may act as aggravators producing cough hypersensitivity. This view has gained considerable support, particularly in Europe. There is no doubt that cough hypersensitivity can be caused by a wide variety of different agents and this can be objectively demonstrated in the laboratory using an inhalation challenge. Upper respiratory tract infections [25], ACE inhibitors [26], and GERD [27] have all been demonstrated to be associated with a change in cough reflex sensitivity. However, while ACE inhibitors alter the sensitivity of the cough reflex, patients with an ACE inhibitor cough give a clinical history similar to patients with cough hypersensitivity syndrome. Thus, the stimulant for the cough reflex hypersensitivity is not one of the precipitants listed above. My belief is that the precipitant of cough hypersensitivity syndrome is reflux, but not the reflux that characterizes GERD. Indeed, heartburn is one of the more weakly associated symptoms of cough hypersensitivity [28]. Here reflux is not necessarily acid and may be of neutral pH, it may be a liquid but is more likely a gaseous mist, and it may be of a short length of exposure. It may not even arise from the stomach but be esophagopharyngeal reflux. This reflux in my view gives rise to hypersensitivity so that reflux precipitates not just coughing but causes the inflammation necessary for the cough hypersensitivity syndrome. Unfortunately, at present no diagnostic test available is capable of proving or disproving this speculation.

To demonstrate the clinical picture of patients with cough hypersensitivity compared to the normal population we undertook a study of 185 consecutive patients attending the Hull Cough Clinic and compared their response to the Hull Cough Hypersensitivity Questionnaire with 70 normal subjects taken from outpatients [29]. There was virtually no overlap between the normal subjects with a mean score of 4/70 and the chronic cough patients with an upper limit of normal of 13/70. This clear separation demonstrates the unique symptom profile of the patients with chronic cough of whatever supposed etiology and demonstrates the homogeneity within the clinic population.

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